A' concl'd

32. (new) The method of claim 24 wherein R^{14} H, and R^{15} is -O-C(O)-CH_2NH_2, -O-C(O)-O-CH_3, -O-C(O)-CH_3 or -SH.

B

Remarks

Applicants have amended the claims to clarify the claimed subject matter and to expedite prosecution. Basis for new claims 11-15 are at least at page 73, lines 11-17 and original claims 1 and 8. Basis for new claim 16 is at least at original claim 2. Basis for new claim 17 is at least at original claim 4. Basis for new claim 18 is at least at original claim 5. Basis for new claims 19-21 is at least at original claims 6 and 7. Basis for new claim 22 is at least at original claim 9. Basis for new claim 23 is at least at original claim 10. Basis for new claims 19-21 is at least at original claims 6 and 7. Basis for new claims 24-32 is at least at page 38, line 4 through page 56 (compound groups 1-11), line 2 and original claim 3. The amendments add no new matter and Applicants request their entry into the record. After entry of the amendments, claims 11-32 are pending.

In the original restriction requirement, the Office required Applicants to select a single species. In their response, Applicants selected 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol as the species. However, the original claims did not include 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol *per se*. Instead, the original claims covered certain analogs of 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol. Applicants apologize for this error. New claim 15 recites a thioether analog of 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol, one of the analogs the original claims included.

35 U.S.C. §112, first paragraph

The Office rejected claims 1-10 under 35 U.S.C. §112, first paragraph, as allegedly not enabled for preventing androgen responsive disease. In casting the rejection, the Office noted that the specification was "enabling for the treatment of an androgen responsive disease" and allegedly did not allow one of skill in the art "to use the invention commensurate in scope with these claims". Applicants respectfully traverse the rejection.

To establish and maintain a rejection under 35 U.S.C. §112, first paragraph, the Office must provide logical reasoning to support its position. The Office must "explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is

inconsistent with the contested statement." *In re Marzocchi and Horton*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). The Office must advance "substantive reasons why the instant specification is non-enabling." "Mere broad generalizations and allegations are insufficient for holding of non-enablement." *Ex parte Goeddel* 5 U.S.P.Q. 2d 1449 (B.P.A.I. 1987). As explained below, Applicants respectfully submit that the rejection is improperly based on a broad allegation, which the Office does not support.

In casting the rejection, the Office did not explain why the present specification, which the Office conceded was enabled for the treatment of androgen responsive diseases, did not teach how to prevent the development of those diseases. Since the claimed methods are sufficient to treat the diseases, there is no basis to assert that those methods are sufficient to prevent the same diseases. Even if a single normal cell were to give rise to two cells capable of causing an androgen responsive disease if they could proliferate, administration of the compound would inhibit further growth, which would prevent disease. Obviously, an androgen driven disease does not arise in a single step or event as a full blown pathological condition in a single day. Such diseases start from a single cell or a limited number of cells, which develop over time to detectable disease. Applicants also note that humans and animals are believed to spontaneously generate malignant and other abnormal cells throughout their life span. However, immune surveillance and other defense mechanisms usually eliminate these cells before they proliferate to detectable levels or cause any detectable disease. Such humans or animals are not considered to be diseased unless and until there has been sufficient cell proliferation to cause a detectable pathology or symptom. Thus, since the claimed methods provide a means to treat the diseases, they will also prevent the diseases by blocking the proliferation needed to cause them.

The discussion above is a rationale that supports Applicant's position that the claimed methods would prevent androgen driven conditions. In view of the foregoing, Applicants respectfully submit that the specification lacks no essential teaching of how to use the claimed invention to prevent the diseases. The rejection does not contain a reasoned argument by the Office to support an allegation of non-enablement and Applicants have provided a logical argument that supports enablement. The rejection should thus be withdrawn. *In re Marzocchi and Horton*, *supra*, *Ex parte Goeddel*, *supra*. Applicants request reconsideration and withdrawal of the rejection.

35 U.S.C. §112, second paragraph

The Office rejected claims 1-10 under 35 U.S.C. §112, second paragraph, as allegedly indefinite in the use of the term "prevent". In casting the rejection, Applicants respectfully traverse the rejection. The term prevent is clear and in common use. Applicants direct the Office's attention to U.S. patent Nos. 6,413,204 (issued July 2, 2002) and 6,395,267 (issued May 28, 2002), both newly cited, and U.S. patent 4,310,523 (issued January 12, 1982), of record and discussed below. These patents use the term "prevent", "prophylaxis" or the like in their claims in the context of preventing disease and none of these patents contain a definition for the terms. The term "prevent" and related terms have been in use for decades and their meanings are obviously clear.

The Office rejected original claims 1, 8 and 9 as indefinite for use of the terms "comprise" and "comprises" with respect to the compounds. The new claims do not contain these terms to describe the compounds and the rejection is moot.

The Office rejected original claim 3 as indefinite for referring to compounds in groups 1 through 13-11. To replace claim 3, Applicants have used the specification at pages 38-56 as a basis for new claims 24-32. These new claims recite some of the compounds that compound groups 1-11 disclose. The new claims are clear and definite and the rejection is moot.

The Office rejected original claim 6 as indefinite for use of the term "second therapy" and original claim 7 as indefinite for use of the term "optionally". New claims 19-21 replace original claims 6 and 7. The new claims do not contain these terms and the rejection should be moot.

The Office rejected original claims 8 and 9 as indefinite for use of improper Markush terminology. The new claims use standard Markush terminology and the rejection should be moot.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. §102(b)

The Office rejected claims 1-10 as allegedly unpatentable over Neumann, U.S. patent No. 4,310,523, of record (hereafter 'Neumann'). Applicants respectfully traverse the rejection as it applies to the new claims. New claims 11-32 all recite the use of a single compound of formula 1 or 2, while Neumann teaches the use of two compounds to prevent or treat the disease. Neumann's teaching of a two compound treatment thus

does not anticipate the new claims. Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. §103(a)

The Office rejected original claims 1-10 as allegedly unpatentable over Chang et al., (P.N.A.S. 96:11173 1999, hereafter "Chang"), Miyamoto et al. (P.N.A.S. 95:11083 1998, hereafter Miyamoto), or Neumann, all of record. Applicants respectfully traverse the rejection as it applies to the new claims.

The Office rejected original claims 1-10 as prima facie obvious over Neumann. As noted above, Neumann teaches a combination therapy that requires the use of an antiandrogen and an antiestrogen, while the present claims recite treatments with a single compound. Neumann does not contain an express suggestion to use a single compound among the disclosed antiandrogens and antiestrogens. Applicants respectfully submit that Neumann alone or combined with Miyamoto or Chang can not sustain a rejection of the new claims under 35 U.S.C. §103(a).

The Office rejected original claims 1-10 as prima facie obvious over Miyamoto. The Office noted that the Miyamoto reference teaches that 3β,17β-dihydroxyandrost-5-ene ("Adiol") has androgenic activity. However, the experimental system that Miyamoto used suggested that Adiol would not be a compound that one would use to treat androgen driven conditions, since a major goal of prostate cancer treatment is inhibiting androgen activity, not enhancing it. In that context, Adiol would not be a candidate compound for treating prostate cancer. Applicants note that the new claims do not include Adiol within their scope.

The Office rejected original claims 1-10 as prima facie obvious over Chang. The Office noted that Chang disclosed that 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol had androgenic activity and alleged that one would be motivated to use the presently claimed compounds to treat an androgen responsive disease. In casting the rejection, the Office has characterized Chang as teaching that one would want to use an androgen to treat the claimed diseases. This may be an error in the interpretation of the reference. Chang describes certain antiandrogen compounds that (1) block the androgenicity of Adiol while (2) having limited androgenic activity themselves. Chang discloses 1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol as an antiandrogen, but does not teach or suggest any derivative of this compound such as a presently claimed ethyl thioether, -S-C_2H_5, analog. Change alone does not provide any motivation to modify the compounds

that Chang discloses to obtain the presently claimed compounds. Neumann and Miyamoto alone or together also do not supply the needed teaching.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Respectfully submitted,

Dated: 8-5-02

Daryl D. Muenchau, Reg. No. 36,616
Hollis-Eden Pharmaceuticals, Inc.
4435 Eastgate Mall, Suite 400
San Diego, CA 92121
P: 858-587-9333
F: 858-558-6470